Utah Diabetes Practice Recommendations

Hyperglycemia Management for Inpatients

Section 3 in a series of topics included in the
Utah Diabetes Practice Recommendations

Diabetes Prevention & Control Program
UTAH DEPARTMENT OF HEALTH

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Hyperglycemia Management for Inpatients

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Dissemination and Review

This section of the Utah Diabetes Practice Recommendations – Hyperglycemia Management for Inpatients, will be distributed to the medical and nursing staff, and the administration at major Utah area hospitals. The currently available body of literature and some important studies clearly indicate that glycemic control in hospitalized diabetic patients and patients experiencing stress-induced hyperglycemia greatly benefit from increased monitoring and treatment to specific glycemic targets.

Medical care facilities and systems will be encouraged to undertake the process of implementing these Recommendations or modifying their existing inpatient protocols to make them more consistent with the protocols contained herein. It is recognized that the target glycemic levels included in these Recommendations, while based on current literature, are still the subject of professional debate.

It is expected that more extensive studies will potentially reduce or increase the exact levels for optimal efficacy. Thus, it is anticipated, due to the lack of long term experience, that the treatment goals contained in this section will require adjustment to greater or lesser degree as more study and experience is gained in the control of inpatient hyperglycemia. In promulgating these Recommendations, it is recognized that while they outline a general course of action for the majority of patients who experience hyperglycemia while in the hospital, they do not substitute for informed clinical judgment on the exact course of treatment for individual patients.

Diabetes and Hyperglycemia Management for Inpatients

INTRODUCTION

Individuals with diabetes have significantly higher hospital admission rates, particularly for conditions related to coronary artery, cerebrovascular and peripheral vascular disease, and infections, nephropathy and lower-extremity amputations. In addition, a recent retrospective review of adult admissions suggested that nearly one third of patients found to have hyperglycemia during hospitalization did not have a prior diagnosis of diabetes. It was found that these patients were more likely to be admitted to the ICU, have longer hospitalizations and higher mortality compared to patients with known diabetes. Evidence is mounting from recent studies that hyperglycemia in the hospital may have serious consequences, and that morbidity and mortality can be reduced through aggressive treatment of hyperglycemia. Unfortunately, the management of the patient's diabetes is often considered secondary to the primary cause of admission, and in patients without a prior diagnosis of diabetes, hyperglycemia is frequently left untreated.

The purpose of this section of the Utah Diabetes Practice Recommendations is to provide insight and management protocols for hyperglycemic screening, treatment and achievement of glycemic targets. It is important to recognize that hyperglycemia in the hospital occurs in three classes of patients:

- Patients with previously diagnosed diabetes known to the treating physician
- Patients with unrecognized diabetes during hospitalization and confirmed as diabetes after discharge, but unknown initially by the treating physician
- Stress hyperglycemia secondary to severe illness occurring during the hospital stay that reverts to normal after discharge

The prevalence of diagnosed diabetes in hospital patients in Utah is reported to be 8.9% based on hospital discharge data, with only 9.8% of these having a principal diagnosis of diabetes. National experts estimate that the true prevalence of diabetes among hospital patients may be underestimated by as much as 40%.

Hyperglycemia and Adverse Outcomes

Research linking hyperglycemia to poor outcomes has centered on the immune system, mediators of inflammation, vascular responses, as well as fluid and electrolyte abnormalities.

- Hyperglycemia has been shown to impair leukocyte chemotaxis, adherence, phagocytosis and intracellular bacteriocidal activity
- Hyperglycemia (and relative insulin deficiency) is pro-inflammatory resulting in the over production of a variety of chemokines and cytokines
- Hyperglycemia contributes to poor wound healing
- Hyperglycemia impairs insulin action (induces insulin resistance) and may transiently or permanently diminish insulin secretion
- Hyperglycemia potentiates the risk of ischemia by altering endothelial function and inducing a pro-thrombotic environment (enhanced platelet activation and reduced fibrinolysis)
- Hyperglycemia causes an obligatory osmotic diuresis that may result in dramatic fluid and electrolyte shifts
- Hyperglycemia has been shown to induce a state of functional gastroparesis
- Untreated (or poorly treated) hyperglycemia in the hospital may provide an unwanted signal to the patient that glycemic management is not important
- Studies examining a possible association among hyperglycemia, endothelial function and outcomes have not yet been done in hospitalized patients despite compelling experimental data
- Acute hyperglycemia is associated with enhanced neuronal damage following induced brain ischemia. A primary link between hyperglycemia and enhanced cerebral ischemic damage appears to be increased tissue acidosis and lactate levels associated with elevated glucose concentrations. Through this mechanism, hyperglycemia appears to cause hypoperfused at-risk tissue to progress to infarction. Many of the same factors that link hyperglycemia to cardiovascular event outcomes likely contribute to acute cerebrovascular outcomes as well.

- The many diverse effects of acute hyperglycemia may well result from the ability of hyperglycemia to produce oxidative stress. Through direct tissue injury or through activation of secondary mediators, hyperglycemia-induced oxidative stress causes cell and tissue injury. Studies have shown that such abnormalities can be reversed by antioxidants or by normalizing blood glucose levels.

Two reliable prospective studies support the relationship between insulin therapy and improved metabolic control and better inpatient outcomes. The first trial was conducted in Belgium and enrolled 1548 critically ill post-operative patients on mechanical ventilation. Patients were randomized to intensive insulin management or to conventional therapy. Those in the intensive management group were placed on an IV infusion of insulin if their random glucose exceeded 110 mg/dL, and the results demonstrated a dramatic reduction in hospital mortality (34%) as well as a marked lowering in episodes of sepsis (46%), hemodialysis (41%) and need for transfusions (50%). The other trial (DIGAMI) was designed to assess whether an acute glucose-insulin infusion during admission for a myocardial infarction in people with diabetes followed by aggressive outpatient management of hyperglycemia using insulin had any influence on survival. Mortality in the intensively treated group was reduced 28-51% at 3 years. A follow-up study by the same investigators, DIGAMI 2, failed to reproduce the results of the first trial; however, the authors point out that DIGAMI 2 was tremendously underpowered due to low enrollment, and there were no differences in glucose control between the groups receiving insulin and the standard treatment arm at any point during the trial. The results were also handicapped because overall mortality was considerably lower than predicted. A subset analysis of another large study, CREATE-ELCA, also failed to support a benefit of glucose-insulin infusion during myocardial infarction, but glucose levels were inadequately controlled during the trial.

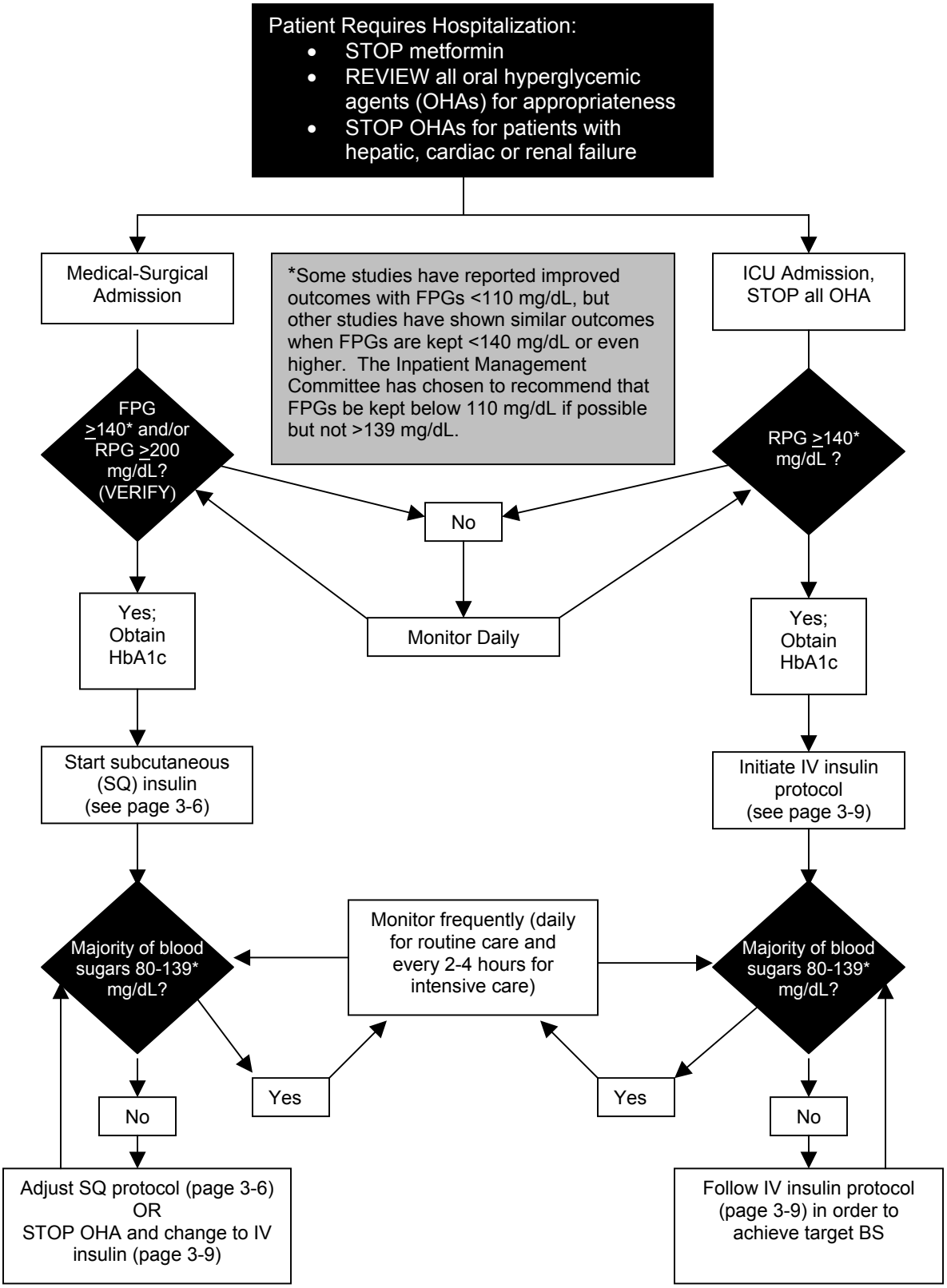
Despite assumptions that insulin attains a benefit indirectly by controlling blood glucose, a growing body of literature raises the question of whether insulin may have direct beneficial effects independent of its effect on blood glucose. Results of a large study of intensive insulin infusion therapy in an intensive care unit, suggest a general anti-inflammatory action of insulin. And these observations have been made repeatedly with smaller trials. These provocative data give the impression that insulin therapy in the inpatient setting has significant potential for benefit. **Because of the numerous contraindications to the use of oral hypoglycemic agents in the hospital, insulin is the clear choice for glucose control in the inpatient setting.**

Increased Morbidity and Mortality Related to Hyperglycemia

Recent observational studies suggest an association exists between hyperglycemia and mortality. In one study of 191 patients undergoing general surgery procedures, it was reported that outcomes correlated with blood glucose levels. Patients with a blood glucose value >220 mg/dL were 5.7 times more likely to experience serious postoperative infections including sepsis, pneumonia, and wound infections than those with blood glucose values <220 mg/dL. In a second study of 1,886 patients, 495 had known diabetes and 223 had “new” hyperglycemia. The new hyperglycemic cohort was likely composed of patients with unrecognized diabetes, prediabetes, and/or stress hyperglycemia secondary to severe illness. After adjusting for confounding factors, patients with new hyperglycemia had an 18-fold increase in hospital mortality and patients with known diabetes had a 2.7-fold increase in mortality compared with the normoglycemic cohort. The observational data from these two studies suggest that hyperglycemia from any etiology in the hospital on general medicine and surgery services is a significant predictor of poor outcomes relative to outcomes for normoglycemic patients. A third study evaluated the hospital care rendered to hyperglycemic individuals who did not have a diabetes diagnosis prior to admission. One third of hyperglycemic surgical patients did not have a diabetes diagnosis at the time of admission even though they had an average peak glucose of 299 mg/dL. While 54% of them received insulin therapy and 59% received bedside glucose monitoring, 66% of daily patient progress notes failed to comment on the presence of hyperglycemia or diabetes. Diabetes was documented in only three patients as a possible diagnosis in daily progress notes. Given the average delay of almost a decade between the onset and diagnosis of type 2 diabetes, further evaluation of hyperglycemia among hospitalized patients presents an important opportunity for earlier detection and treatment.

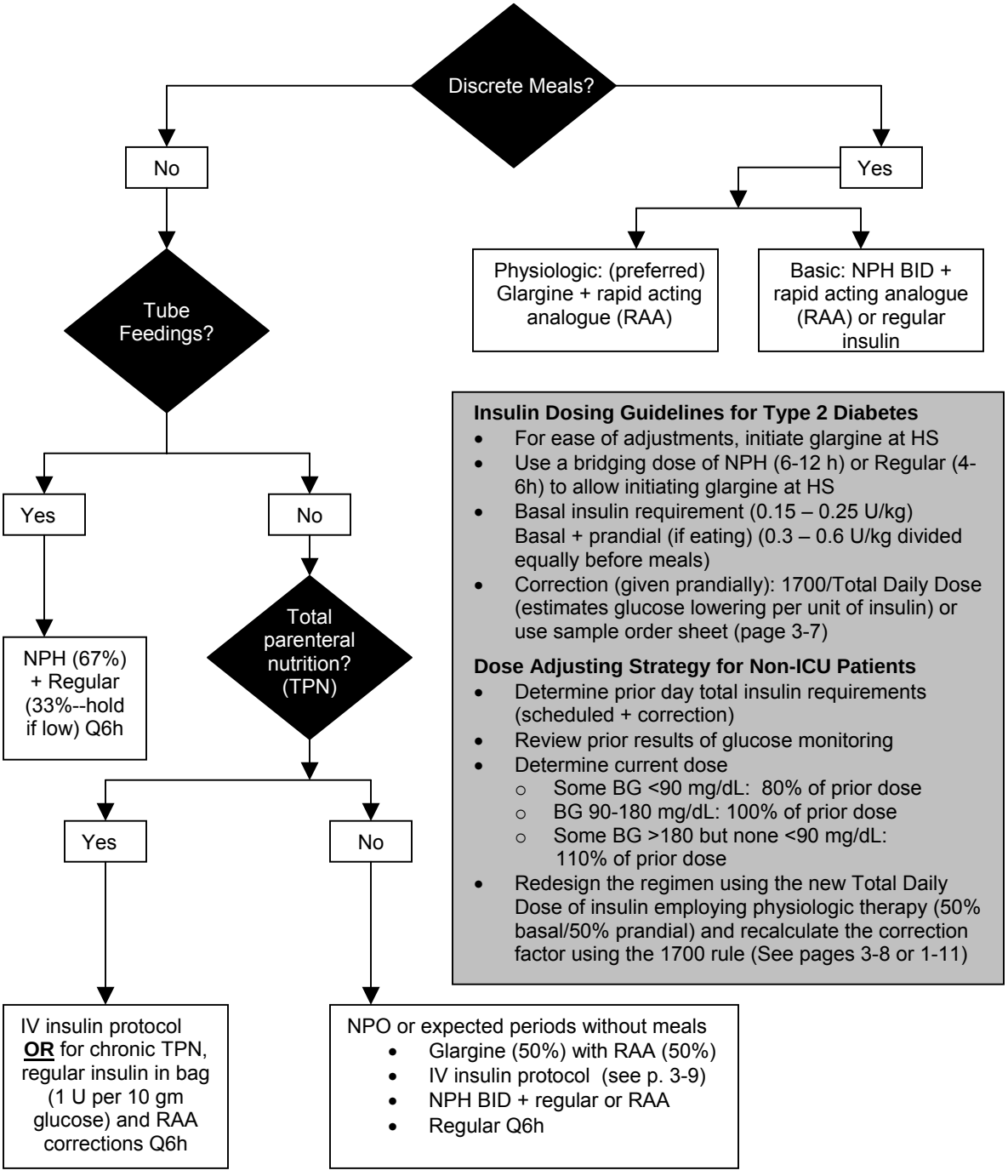
The information and algorithms that follow in this section are based on the best available published opinion and represent the current understanding of these issues. In the absence of definitive data, the committee based some of its recommendations on its own consensus opinions.

INITIAL HYPERGLYCEMIA EVALUATION



SUBCUTANEOUS INSULIN PROTOCOL

- Please keep in mind that not every contingency can be anticipated and an individual's response cannot be predicted. Edema and hypotension may alter SQ insulin absorption kinetics resulting in unexpected or cumulative effects.
- The use of "sliding scale" insulin therapy has been associated with a higher incidence of adverse metabolic outcomes and should be abandoned.
- Inpatient insulin regimens should be designed using the basal-bolus concept. These physiological regimens consist of scheduled therapy (basal insulin and planned meal-related bolus insulin) and correction therapy to address deviations in glycemic control. The typical inpatient regimen is approximately 85% scheduled therapy and 15% correction therapy.



Insulin Dosing Guidelines for Type 2 Diabetes

- For ease of adjustments, initiate glargine at HS
- Use a bridging dose of NPH (6-12 h) or Regular (4-6h) to allow initiating glargine at HS
- Basal insulin requirement (0.15 – 0.25 U/kg)
  Basal + prandial (if eating) (0.3 – 0.6 U/kg divided equally before meals)
- Correction (given prandially): 1700/Total Daily Dose (estimates glucose lowering per unit of insulin) or use sample order sheet (page 3-7)

Dose Adjusting Strategy for Non-ICU Patients

- Determine prior day total insulin requirements (scheduled + correction)
- Review prior results of glucose monitoring
- Determine current dose
  - Some BG <90 mg/dL: 80% of prior dose
  - BG 90-180 mg/dL: 100% of prior dose
  - Some BG >180 but none <90 mg/dL: 110% of prior dose
- Redesign the regimen using the new Total Daily Dose of insulin employing physiologic therapy (50% basal/50% prandial) and recalculate the correction factor using the 1700 rule (See pages 3-8 or 1-11)

SAMPLE ORDER SHEET

1. Check Blood glucose (BG)

☐ Before meals and at bedtime

☐ Every 6 hours (Patients who are NPO or getting tube feeds)

☐ Other

2. Scheduled Insulin

Insulin	Breakfast	Lunch	Dinner	Bedtime
Basal Insulin	Give _____ units ☐ glargine (Lantus) ☐ NPH	→ → **OR**	Give _____ units → → → ☐ NPH → **OR** →	Give _____ units ☐ glargine (lantus) ☐ NPH
Prandial Insulin	Give _____ units ☐ Lispro (Humalop) ☐ Aspart (Novolog) ☐ Regular	Give _____ units ☐ Lispro (Humlog) ☐ Aspart (Novolog) ☐ Regular	Give _____ units ☐ Lispro (Humlog) ☐ Aspart (Novolog) ☐ Regular	

3. Correction Insulin Algorithm (choose an insulin and dose)

☐ **Lispro (Humalog)** ☐ **Aspart (NovoLog)** ☐ **Regular**

- Add 1 unit for each _____ mg/dL above the preprandial target of ____ mg/dL
- Subtract 1 unit from the scheduled prandial bolus for each _____ mg/dL below the target of _____ mg/dL.
- Overnight or HS correction is one-half of the daytime correction dose.

4. Hypoglycemia protocol

A. For patients who can take PO, give 20g of fast acting carbohydrate: e.g. 6 oz fruit juice or regular soda; 12 oz low fat milk

B. If patient cannot take PO, give 25 cc of D50 IV push

C. If IV access is not available, give 1mg glucagon IM

D. Check blood glucose (BG) q15 minutes and repeat until BG >100

E. Notify provider when BG is >100 to determine if dose adjustment of scheduled insulin is warranted

Transition from Intravenous (IV) to Subcutaneous (SQ) Insulin Protocol

Plan SQ regimen in terms of basal and bolus (scheduled insulin) and correction doses (given in conjunction with meal-related bolus). In order to determine an appropriate starting dose of subcutaneous insulin, it is crucial to differentiate whether the IV insulin infusion is simply covering basal insulin requirements or if it has been used to cover nutritional needs as well.

Example 1 - IV Insulin Covers Only Basal Insulin Requirements:
If the IV infusion is simply covering basal insulin needs, use 80% of the 24 hour requirement and give it as glargine and add prandial insulin as the patient's appetite improves. Estimate **prandial insulin requirements** by dividing the number of units of the glargine dose by 3 and administering this amount of rapid acting analog (RRA) with each meal. **Correction doses** (estimation of the amount of glucose lowering per unit of insulin) are calculated as 1700/TDD (total daily dose) and are administered with meals based upon target glucose values. **[See 1700 Rule (1500 in earlier editions) on page 1-11]**

Example 1

Patient is NPO, has received 2 U/h IV insulin for the past 6 hours, glucose values are stable

1. Calculate basal insulin requirements: **2U/h x 24 hours = 48 U**
   48 U x 80% = 38 U basal SQ insulin
2. Calculate prandial insulin requirements: **38/3 ~ 13 U of prandial insulin with meals**
3. Calculate correction dose: **Tally total daily dose (TDD) 38 U + 38 U = 76 U**
   1700/76 = 22 (round to a convenient number like 25)
   - 1 U is expected to lower BG ~25 mg/dL given prandially as correction dose (page 1-11)
4. Suggested regimen: **Basal dose = 38 U glargine given at HS**
   Prandial dose = 13 U RAA with each meal (if patient is eating normally; otherwise give lower amounts and gradually increase dose as needed)

Example 2 - IV Insulin Covers Both Basal Requirements and Nutritional Needs:
Estimate 24-hour insulin requirements (total daily insulin dose or TDD) based upon the average amount of insulin infused during the preceding 6-8 hours. This assumes stable levels of blood glucose and no pressor requirements. Use 80% of this amount as the new scheduled total daily dose (TDD) and give 50% as basal insulin (glargine preferred or NPH in 2 divided doses). The basal insulin should be administered SQ two hours prior to discontinuing the IV insulin infusion. The remaining 50% is given as a rapid acting analog (RAA), divided equally by the number of daily meals, and given prandially.

Example 2

Patient received 3 U/h IV insulin for past 8 hours, glucose values are stable at 95-105 mg/dL

1. Calculate Total Insulin Requirements: **3 U/h x 24 hours = 72 U**
2. Calculate Total Daily Insulin Dose (TDD): **72 U x 80% = 58 U (TDD)**
3. Calculate Corrections Dose: **1700/58 = 29 (1 U expected to lower BG ~30 mg/dL)**
   - Add 1 U of rapid acting analog (RAA) to scheduled prandial bolus for each ~ 30 mg/dL (rounded to a convenient value) elevation in blood glucose above pre-prandial target, for example 110 mg/dL
   - Subtract 1 U of RAA from scheduled prandial bolus for each ~30 mg/dL below preprandial target
   - Overnight corrections should be made cautiously. The committee recommends using one-half of the daytime correction dose with appropriate glycemic monitoring
4. Calculate Scheduled Insulin dose **Basal dose = 58 U x 0.5 ~ 30 U (Give HS as glargine)**
   Prandial dose = 30/3 = 10 U
   (Give as RAA with meals)

Discharge Plans

To differentiate "hospital hyperglycemia" from newly diagnosed diabetes, use the HbA_{1C} obtained on admission

- HbA_{1C} < 5.2% is consistent with "hospital hyperglycemia"
- HbA_{1C} > 6.0% is likely consistent with a diagnosis of diabetes

INTRAVENOUS INSULIN PROTOCOL (Yale Protocol)

The clinical effectiveness of the Yale protocol is well established in the medical literature (Diabetes Care 27: 461-467, 2004). Adjustments to the infusion rate are determined from the protocol's 2 tables. The protocol is simple and easily applicable once its underlying principles are understood. In the tables below, Δ = the change (decrease or increase) in the insulin infusion rate, and 2 Δ = a doubling of the change in the infusion rate.

Table 1:

BG 75-99 mg/dL	BG 100-139 mg/dL	BG 140-199 mg/dL	BG ≥ 200 mg/dL	INSTRUCTIONS
		BG ↑ by >50 mg/dL/hr	BG ↑	↑ INFUSION BY "2 Δ"
	BG ↑ by >25 mg/dL/hr	BG ↑ by >1-50 mg/dL/hr *OR* BG UNCHANGED	BG UNCHANGED *OR* BG ↓ by 1-25 mg/dL/hr	↑ INFUSION BY " Δ "
BG ↑	BG ↑ by >25 mg/dL/hr BG UNCHANGED *OR* BG ↓ by 1-25 mg/dL/hr	BG ↓ by 1-50 mg/dL/hr	BG ↓ by 26-75 mg/dL/hr	NO INFUSION CHANGE
BG UNCHANGED *OR* BG ↓ by 1-25 mg/dL/hr	BG ↓ by 26-50 mg/dL/hr	BG ↓ by 51-75 mg/dL/hr	BG ↓ by 76-100 mg/dL/hr	↓ INFUSION BY " Δ "
BG ↓ by >50 mg/dL/hr	BG ↓ by >50 mg/dL/hr	BG ↓ by >75 mg/dL/hr	BG ↓ by >100 mg/dL/hr	HOLD X 30 MIN, THEN ↓ INFUSION BY "2 Δ"

Table 2:

Current Rate (U/hr)	Δ = Rate of Change (U/hr)	2 Δ = 2 x Rate Change (U/hr)
<3.0	0.5	1
3.0–6.0	1.0	2
6.5–9.5	1.5	3
10.0–14.5	2.0	4
15.0–19.5	3.0	6
20.0–24.5	4.0	8
≥ 25	≥5.0	10 (consult ordering physician)

Starting the Infusion:
Dividing the starting blood glucose by 100 and rounding to the nearest half unit determines the initial bolus and infusion rate.

Example: If the starting glucose is 255 mg/dL (255 ÷ 100 = 2.55; round to 2.5). Give 2.5 units as an IV bolus and start the insulin infusion at 2.5 units/hour

PRINCIPLE 1: The rate of the insulin infusion is affected by the difference between the current and goal glucose values. The greater the difference between the current and goal values, the greater will be the corresponding rate of insulin infusion. This principle directs the selection of the column in Table 1. The higher the current blood glucose level, the further to the right in the table is the applicable column.

Example: If the current blood glucose were 195 mg/dL, the third column would be selected.

BG 75-99 mg/dL	BG 100-139 mg/dL	BG 140-199 mg/dL	BG ≥ 200 mg/dL	INSTRUCTIONS
		BG ↑ by >50 mg/dL/hr	BG ↑	↑ INFUSION BY "2 Δ"
	BG ↑ by >25 mg/dL/hr	BG ↑ by >1-50 mg/dL/hr *OR* BG UNCHANGED	BG UNCHANGED *OR* BG ↓ by 1-25 mg/dL/hr	↑ INFUSION BY " Δ "
BG ↑	BG ↑ by >25 mg/dL/hr BG UNCHANGED *OR* BG ↓ by 1-25 mg/dL/hr	BG ↓ by 1-50 mg/dL/hr	BG ↓ by 26-75 mg/dL/hr	NO INFUSION CHANGE
BG UNCHANGED *OR* BG ↓ by 1-25 mg/dL/hr	BG ↓ by 26-50 mg/dL/hr	BG ↓ by 51-75 mg/dL/hr	BG ↓ by 76-100 mg/dL/hr	↓ INFUSION BY " Δ "
BG ↓ by >50 mg/dL/hr	BG ↓ by >50 mg/dL/hr	BG ↓ by >75 mg/dL/hr	BG ↓ by >100 mg/dL/hr	HOLD X 30 MIN, THEN ↓ INFUSION BY "2 Δ"

PRINCIPLE 2: The direction and rate of the change (mg/dL/hour) in blood glucose affect the rate of the insulin infusion. The need to change the insulin infusion (increase or decrease) will be determined in part by the direction of change in the glucose values (increasing, remaining unchanged, or decreasing). The magnitude of the change in the infusion rate will be influenced by the rate of change in the given direction, e.g. if the glucose values are rising rapidly, a larger change in rate will be needed than if they are rising slowly. Principle 2 directs the selection of the cell in Table 1 once the column has been selected.

After the cell has been selected, the last column on the right side of the table indicates whether "No Infusion Change", a small change "Δ" or a large change "2Δ" should be made.

Example: If the blood glucose is 195 mg/dL and the glucose value is decreasing by 60 mg/dL/hour, then the cell indicated in the chart below would be selected. Based on the instructions from the right hand column, a small "Δ" decrease would be needed in the infusion rate.

BG 75-99 mg/dL	BG 100-139 mg/dL	BG 140-199 mg/dL	BG ≥ 200 mg/dL	INSTRUCTIONS
		BG ↑ by >50 mg/dL/hr	BG ↑	↑ INFUSION BY "2 Δ"
	BG ↑ by >25 mg/dL/hr	BG ↑ by >1-50 mg/dL/hr *OR* BG UNCHANGED	BG UNCHANGED *OR* BG ↓ by 1-25 mg/dL/hr	↑ INFUSION BY " Δ "
BG ↑	BG ↑ by >25 mg/dL/hr BG UNCHANGED *OR* BG ↓ by 1-25 mg/dL/hr	BG ↓ by 1-50 mg/dL/hr	BG ↓ by 26-75 mg/dL/hr	NO INFUSION CHANGE
BG UNCHANGED *OR* BG ↓ by 1-25 mg/dL/hr	BG ↓ by 26-50 mg/dL/hr	BG ↓ by 51-75 mg/dL/hr	BG ↓ by 76-100 mg/dL/hr	↓ INFUSION BY " Δ "
BG ↓ by >50 mg/dL/hr	BG ↓ by >50 mg/dL/hr	BG ↓ by >75 mg/dL/hr	BG ↓ by >100 mg/dL/hr	HOLD X 30 MIN, THEN ↓ INFUSION BY "2 Δ"

PRINCIPLE 3: The rate of change in the infusion rate is affected by the current rate of infusion. The size of a small "Δ" or a large "2Δ" adjustment in the insulin infusion rate is determined by the amount of the current infusion rate. The larger the current rate of infusion, the larger the change that is required to influence the glucose values. The absolute change in infusion rate is found in Table 2.

Example: If the current insulin infusion rate were 8 units/hour, what would the new infusion rate be after a small "Δ") decrease in the rate?

Current Rate (U/hr)	Δ = Rate of Change (U/hr)	2 Δ = 2 x Rate Change (U/hr)
<3.0	0.5	1
3.0–6.0	1.0	2
6.5–9.5	1.5	3
10.0–14.5	2.0	4
<15.0–19.5	3.0	6
<20.0–24.5	4.0	8
≥ 25	≥5.0	10 (contact ordering provider)

The new rate would be 8 – 1.5 = 6.5 units per hour.

Summary: By applying these principles to the two tables of the Yale protocol, accurate effective changes may be made to the insulin infusion rate to achieve optimal blood glucose control.

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